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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/686,092	10/14/2003	Karen W. Shannon	10030468-1	6820

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EXAMINER	
WHALEY, PABLO S	
ART UNIT	**PAPER NUMBER**
1631	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/686,092	SHANNON, KAREN W.	
	Examiner	Art Unit	
	Pablo Whaley	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-20 and 26-30* is/are pending in the application.

4a) Of the above claim(s) *17-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 6-16 and 26-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

NON-ELECTED INVENTION

Amended claim 17 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Applicant's election with traverse of Group I (Claims 1-16) in the reply filed on 05/31/2006 is noted. Group I is directed to a method of identifying a sequence of a nucleic acid. Unlike Group I, claim 17 (Group II), while amended to recite method steps related to Group I, remains directed to a method of "producing a nucleic acid array" and results in a product. Thus, Group I and II are distinct as they are directed to different effects, and the methods as claimed are not obvious variants. See MPEP § 806.05(j). Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 17 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. For these reasons, Group I and Group II are not rejoined and the FINALITY of this requirement is still deemed proper.

Claims 17-20 are hereby withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention or species, there being no allowable generic or linking claim.

CLAIMS UNDER EXAMINATION

Claims herein under examination are claims 1-4, 6-16 and 26-30. Claims 26-30 are newly added. This application contains claims 17-20 drawn to an invention nonelected with traverse in

the response filed 05/31/2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied, as necessitated by amendment. They constitute the complete set presently being applied to the instant application.

CLAIM REJECTIONS - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Newly added claims 26-30 are rejected under 35 U.S.C. 101 because these claims are drawn to non-statutory subject matter. This rejection is necessitated by amendment. A statutory process must include a step of a physical transformation of matter, or produce a concrete, tangible, and useful result [State Street Bank & Trust Co. v. Signature Financial Group Inc. CAFC 47 USPQ2d 1596 (1998)], [AT&T Corp. v. Excel Communications Inc. (CAFC 50 USPQ2d 1447 (1999)].

Claims 26-30 are directed to a method for identifying a sequence of nucleic acid that is suitable for use as a substrate surface immobilized normalization probe, which does not recite either a physical transformation of matter nor a practical application [i.e. concrete, tangible, and useful result]. Claim 26 recites steps comprising identifying probe sequences, empirically evaluating probe sequences, clustering probe sequences, evaluating non-clustering probes, and recording probe sequences on a computer-readable medium. Therefore, the instant claims

encompass non-physical (i.e. *in-silico*) method steps which do not result in a physical transformation of matter. Where a claimed method does not result in a physical transformation of matter, it may be statutory where it recites a result that is concrete (i.e. reproducible), tangible (i.e. communicated to a user), and useful result (i.e. a specific and substantial). In the instant case, claims 26-30 do not recite a tangible result such that it is useful to one skilled in the art. For these reasons, the instant claims are not statutory.

This rejection could be overcome by amending the claims to recite that a result of the method is "displayed" or "outputted" (e.g. output to a user, a display, a memory, or another computer, etc.), or by amending the claims to include a step of a physical transformation of matter (e.g. assay). For an updated discussion of statutory considerations with regard to non-functional descriptive material and computer-related inventions, see the Guidelines for Patent Eligible Subject Matter in the MPEP 2106, Section IV.

CLAIM REJECTIONS - 35 USC §112, 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Applicant's arguments, filed 11/02/2006, have not addressed every aspect of the Examiner's rejection as set forth in the previous office action and discussed below. This rejection is therefore maintained and reiterated, and newly applied to claims 26-30 as necessitated by amendment.

Claims 1-4, 6-16 and 26-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in *In re Wands*, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breath of the claims. While all of these factors are considered, a sufficient amount for a prima facie case are discussed below which leads to the determination that the above claim lacks enablement due to undue experimentation being required to make and use the invention.

Amended claim 1 and newly added claim 26 are directed to methods of identifying a sequence of a nucleic acid that is suitable for use as a substrate surface immobilized normalization probe. Claims 1 and 26 recite steps of (i) identifying a plurality of candidate probe sequences based on selection criteria, (ii) empirically evaluating probe sequences under different experimental conditions, (iii) clustering probe sequences based on empirical data values, and (iv) and evaluating any remaining non-clustering probes for candidate probe sequences. In the instant case, the claimed subject matter lacks enablement for the following reasons:

Regarding step (ii), instant claim 1 now requires a plurality of different experimental conditions to obtain a collection of empirical data values for each of said candidate nucleic acid probe sequences for each of said plurality of different experimental conditions. Given the nature of the invention, identifying a sequence of a nucleic acid that is suitable for use as a substrate surface immobilized normalization probe based on steps (i)-(iv) generally requires the evaluation of gene expression data. However, such limitations are not reflected in the instant claims [Wands factors (2), (3)].

Regarding steps (iii), instant claim 1 requires clustering candidate probe sequences into one or more groups of candidate probe sequences based on empirical values. While the specification does provide a working example [p.32], this example is directed to gene expression experimental data, and thus does not provide sufficient guidance as to how to cluster candidate probe sequence in groups where one or more groups exhibits substantially the same performance across experimental sets based on empirical values. Again, the specification fails to define the metes and bounds of what constitutes "empirical values," and how one of ordinary skill in the art would identify or obtain the appropriate "empirical values" given the lack of description regarding the terms. [Wands factors (2), (4), (8)].

Regarding step (iv), instant claim 1 results in "evaluating any remaining non-clustering probes for candidate probe sequences that satisfy a signal intensity threshold and exhibit no signal variation." Applicant's arguments that the specification [p.23] provides sufficient disclosure address the evaluation of non-clustering probe sequences for suitability has been fully considered. However, the specification [p.23, lines 16-20] discloses limitations (i.e. signal intensities provided by resultant non-clustering candidate probes) that are not recited to the instant claims. Therefore, it remains unclear how said candidate probes sequences that satisfy a signal intensity threshold are used to evaluate non-clustering probes as no correlation has

been set forth in the instant claims relating non-clustering probes to signal intensity data. Secondly, as no steps directed to obtaining or identifying probes that are "non-clustering" are recited in the instant claims, it is unclear how the evaluation of "any" remaining non-clustering probes "for candidate sequences" results in the identification of candidate probes sequences that are suitable for use as a substrate surface immobilized normalization probe. Thirdly, it is unclear how the "non-clustering probes" are being evaluated. The specification fails to define the metes and bounds of what constitutes "evaluating" such that one of ordinary skill in the art would known how to identify probe sequences that are suitable for use as a normalization probe.

Methods of clustering analysis applied to gene expression data are well-known in the art [Ben-dor et al., Journal of Computational Biology, 1999, Vol. 6, No. ¾, p. 281-297] and [Alon et al., Cell Biology, 1999, Vol. 96, p.6745-6750]. Such methods disclose steps directed to (i) determination of gene expression data by measuring expression levels experimentally (ii) calculation of similarity matrices comprising expression patterns, (iii) clustering gene based on similarity data or expression data (i.e. intensity data) using clustering algorithms, and (iv) representing constructed solutions visually as histograms or distributions. Furthermore, most clustering analysis experiments consist of some comparative steps (e.g. mutants compared to a reference) and evaluation of data using some statistical correlation methods as well. Kane et al. [Nucleic Acids Research, 2000, Vol. 28, p.4552-4557], for example, teach methods of oligonucleotide probe design and assessment, including steps comparison of probe sensitivities [Fig. 1]. Thus, specification does not provide sufficient guidance as to how to identify a sequence of a nucleic acid that is suitable for use as a substrate surface immobilized normalization probe based on clustering of candidate probe sequences [Wands factors (1), (2), (6), (7)].

Despite the high level of skill in the art, as the specification does not disclose sufficient guidance as to how one of skill in the art can identify a sequence of a nucleic acid that is suitable for use as a substrate surface immobilized normalization probe, and as the instant claims do not recite steps consonant with the identification of a sequence of a nucleic acid, as set forth above, it would require undue experimentation by one of skill in the art to predictably practice the instantly claimed invention. [Wands factors (1), (2), (6), (7)].

CLAIM REJECTIONS - 35 USC § 112, 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 6-16 and 26-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following rejections are either reiterated or newly applied, as necessitated by amendment.

Applicant's arguments, filed 11/02/2006, that "non-clustering probes" have antecedent basis in view of claim 1, step c, which recites "clustering said candidate probes into one or more groups" is not persuasive. This rejection is maintained and , as claim 1, step c, is clearly directed to "clustering" of data into groups of candidate probe sequences, and thus does not provide implicit or explicit support for any steps or limitations directed to obtaining "non-clustered" data. Claim 1, step (d), recites the limitation "evaluating any remaining non-clustering probes." As there is no previous recitation of non-clustering probes or any step directed to obtaining "non-clustering probes", there is lack of antecedent basis for this limitation.

Furthermore, it is unclear in what way this limitation further limits the said candidate probes. Clarification is requested.

Applicant's arguments, filed 11/02/2006, that "for candidate probe sequences that satisfy a signal intensity threshold and exhibit substantially no variation in signal" provides basis for the method for "evaluating any remaining non-clustering probes" is not persuasive. This rejection is maintained and reiterated, as this limitation is directed to the nature of the candidate probe sequences, per se, has no restrictive effect on the "evaluation of any remaining non-clustering probes." Claim 1, step (d), recites the limitation "evaluating any remaining non-clustering probes." It is still unclear whether said non-clustering probes are being directly evaluated based on signal intensity threshold, signal variation, or some other method. Clarification is requested.

Applicant's arguments, filed 11/02/2006, that selection criteria of claim 2 further limit claim 1 are not illuminating. This rejection is maintained and clarified. Claim 3 recites the limitation "the method according to claim 2, wherein all three of said selection criteria...are employed is said identifying step (a)." Claim 3 requires criteria (i), (ii), and (iii), making claim 3 broader in scope than claim 2. Thus it remains unclear in what way the steps of claim 3 further limit claim 2. Furthermore, the Examiner believes applicant should correct this limitation to recite "wherein...selection criteria...are employed in said identifying step (a)." Correction is again requested.

Applicant's arguments, filed 11/02/2006, with regards to "/" meaning "the alternative" are not illuminating. This rejection is maintained and clarified. Claim 6 recites the limitation "each member...is a different tissue/cell line differential gene expression assay." It is unclear whether each member is a different tissue, or a different cell line differential gene expression assay, or a different differential gene expression assay, or a combination of these. Clarification is again requested via clearer claim language.

Applicant's arguments, filed 11/02/2006, that claim language conveys a "decision making process employed by the person using the claim" are not illuminating. This rejection is maintained and clarified, as applicant is arguing features that are not recited in the rejected claim(s). Claim 10 recites the limitation "wherein a candidate probe sequence is considered to exhibit." It is unclear whether "considered to exhibit" is intended to be an active method step or a further limitation of said probe sequence. Clarification is again requested.

Newly added claim 26, step (d), recites the limitation "evaluating any remaining non-clustering probes." As there is no previous recitation of non-clustering probes or any step directed to obtaining "non-clustering probes", there is lack of antecedent basis for this limitation. It is noted that claim 26, step c, recites "clustering" of data into groups of candidate probe sequences. However this does not provide basis for steps or limitations directed to obtaining "non-clustered" data. Clarification is requested. Claims 27-30 are rejected as they depend directly from claim 26.

CONCLUSION

No Claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pablo Whaley whose telephone number is (571)272-4425. The examiner can normally be reached on 9:30am - 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached at 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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